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Interestingly, cardiac myocytes transfected with Daam1 siRNA contract at a rate approximately three times higher than control treated myocytes, suggesting that Daam1 regulates cardiac contractility. Thus, Daam1 regulates cardiomyocyte cell–cell interactions and may be required for late stage remodeling in the heart.

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Program/Abstract # 130
LR asymmetric morphogenesis of heart looping
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Establishment of left right (LR) axis formation is required for correct positioning and function of internal organs. Our long-term goal is to reveal the mechanism of how LR asymmetric signals regulate LR asymmetric morphogenesis. Our previous work has revealed the significance of the Nodal-signaling pathway in the establishment of the LR asymmetry, which is required for the correct positioning and morphogenesis of internal organs. However, the cellular and molecular mechanisms by which LR signals bring about asymmetric organ development are unknown. We are investigating how LR signals regulate cell behaviors in asymmetric heart looping morphogenesis. The heart is the first organ to exhibit LR asymmetry, and its looping morphogenesis is readily accessible in culture. The left and right primordial heart fields migrate and fuse to form a single heart tube that subsequently loops rightward. Looping morphogenesis is achieved by rotation of the heart tube exerted by the out flow tract rotation and overriding of left caudal rudiments. We focus on cellular behaviors in these events and have analyzed cell movement by dye labeling and morphological changes by time lapse imaging, cell proliferation, and gene expression in the chick and mouse. Our cell tracing experiments showed changes in cell positions from mediolateral to anteroposterior orientation, and significant cell cluster extension during migration, which could be major forces for looping morphogenesis. Based on these data, we will discuss how LR signals regulate LR asymmetric looping of the heart.

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Program/Abstract # 131
Inturned PCP effector gene is required for cilia biogenesis and mouse embryonic development
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Cilia are cell surface organelles required for mammalian embryonic development and multiple adult physiological functions. Recent protein localization studies indicated that some proteins regulating the planar cell polarity (PCP) pathway are localized to the axonemes and basal bodies of the primary cilia. However, the functional significance of this connection between cilia and PCP regulation has yet to be corroborated in mammals. The inturned PCP effector (Intu) gene was originally identified in the fruit flies based on its role in regulating the formation and polarity of wing hairs. In the current study, we take both forward and reverse genetic approaches to study the function of Intu in the mouse. Double-thumb (Dtm), a hypomorphic mutant allele of Intu generated by chemical mutagenesis, exhibits polydactyly and behavioral defects including circling and head bobbing. We also generated a null Intu mutant through gene-targeting in mouse embryonic stem (ES) cells, and found that the complete loss of Intu function results in multiple developmental defects including neural tube defects, spinal cord patterning defects and severe polydactyly. Our scanning electron microscopic study indicated that cilia biogenesis is disrupted by the mutation in Intu. In conclusion, our study provided the first evidence in the mouse that a PCP effector gene is required for ciliogenesis and embryonic development.

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Program/Abstract # 132
Patterning of the mouse embryonic germ layers: The Townes and Holtfreter cell sorting experiments revisited
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The experiments undertaken by Townes and Holtfreter described that cells dissociated from the embryonic germ layers segregated homotypically once homogeneously mixed. Subsequently, Steinberg pioneered the differential adhesive hypothesis (DAH) to explain these and other patterning phenomena. We have revisited these issues using embryoid bodies derived from mouse embryonic stem (ES) cells where nascent endoderm is distributed, initially internally but eventually sorts to the spheroid surface. Wild type and E-cadherin null ES cells were used to generate chimeric embryoid bodies to probe the relative importance of adhesion and differentiation for the partitioning of endoderm to surface. When undifferentiated wild type and undifferentiated E-cadherin null ES cells were mixed, the resulting cell aggregates consisted of a core of highly adhesive wild type cells surrounded by E-cadherin null cells, consistent with the DAH. Both ES cell types were also differentiated into primitive endoderm-like cells by exposure to retinoic acid and then mixed with undifferentiated counterparts. We observed that endoderm cells always sorted to the surface to form an endoderm layer irrespective of their E-cadherin status or that of their undifferentiated counterparts. Thus, the sorting of primitive endoderm from pluripotent ES cells contradicts the DAH. We propose that the autonomous ability of endoderm cells to generate apical polarity, rather than differential adhesive affinity, governs the developmental restriction of primitive endoderm cells to a superficial layer.

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Program/Abstract # 133
Sequential roles of Wnt signaling/β-catenin in mouse ventral dermal development
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The dermis promotes the development and supports functional components of skin such as hair follicles, sweat glands, nerves, and blood vessels. In the chick, the dermis originates from the somites, the lateral plate mesoderm, and cranial neural crest. Despite the importance of dermis in the structural and functional integrity of the skin, genetic analysis of dermal development in different parts of the embryo is incomplete. First, we show that mouse ventral dermis originates from the lateral plate mesoderm. Next, we demonstrate that Wnt/β-catenin signaling is active and necessary during the development of ventral dermal cells. Loss of β-catenin function in the flank mesenchyme leads to the absence of ventral dermis in the mouse embryo. Wnt/β-catenin signaling is required for cell survival and is sufficient for mouse ventral dermal cell specification. Despite the different origins of dorsal and ventral dermal cells, this study reveals new roles for β-catenin/Wnt signaling during early dermal cell development. This is the first study to define the origin and signaling requirement of mammalian ventral dermis.

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Program/Abstract # 134
Role of nectins in the development of epithelial appendages
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Nectins are immunoglobulin-like cell adhesion proteins which function in cell–cell junctions and cell–cell contacts. Mutations in the nectin-1 gene are responsible for a rare human syndrome characterized by ectodermal dysplasia (ED), cleft lip and palate, and limb defects. The nectin-1 null mutant mice were reported to have a mild defect in epidermal stratification [Wakamatsu et al. J. Biol. Chem. 2007 282:18173–81] and our analysis revealed additionally a subtle defect in the formation of dental enamel but we did not detect other obvious phenotypes. In order to explore the possibility that the function of nectin-1 is compensated by nectin-3, we first compared their expression patterns. In E15 mouse embryos nectin-1 was expressed in the suprabasal layer of epidermis. Nectin-1 and nectin-3 were coexpressed in the inner root sheath of hair follicles and in the stellate reticulum cells of the tooth buds. We then generated nectin-1 and nectin-3 double null mutant mice. They exhibited characteristics of human ED patients, including skin, tooth, hair and limb abnormalities. I will present the phenotypic analysis of the nectin-$1^{-/-}$; nectin-$3^{-/-}$ mice. These results suggest that nectin-1 and nectin-3 are required for the development of epidermis and epithelial appendages, and that the necessary function of nectin-1 in humans is partially compensated by nectin-3 in the mouse.

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Program/Abstract # 135
Fgfr2b signaling integrates tooth morphogenesis and dental axon patterning
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Dental trigeminal nerve fiber growth and patterning are strictly integrated with tooth morphogenesis, but it is still unknown, how these two developmental processes are coordinated. We show that targeted inactivation of the dental epithelium expressed Fgfr2b results in cessation of the mouse molar tooth development at the degenerated cap stage and the failure of the trigeminal molar nerve to establish the lingual branch at while the buccal branch develops properly. This axon patterning defect correlates to the histological absence of the mesenchymal dental follicle and adjacent Semaphorin3A-free dental follicle target field as well as appearance of ectopic Sema3A expression domain in the lingual side of the tooth. Tgfbeta1, which controls Sema3A, and Fgf4, which induced Tgfbeta1, were absent from the Fgfr2b (−/−) tooth. Fgf4 beads rescued Tgfbeta1 in the Fgfr2b(−/−) and Tgfbeta1 induced de novo Sema3A in the dental mesenchyme. Collectively these results demonstrate that epithelial Fgfr2b, by mediating local epithelial–mesenchymal interactions, integrates tooth morphogenesis and dental axon patterning during odontogenesis.

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Program/Abstract # 136
Development of successional teeth
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The epithelial thickening in the oral epithelium is the first stage of tooth development. This thickening grows deeper into the mesenchyme and forms the dental lamina. Here, we focus on differences in dental lamina development between monophyodont, diphyodont and polyphyodont species. Mouse, as the main model for tooth developmental study, forms only one tooth generation. The dental lamina stage is reduced in time and shortly after lamina establishing, individual epithelial anlagen bud off to form distinctive teeth. In the contrast, pig with two generations of teeth, develops well-established dental lamina that protrude deeply into mesenchyme. In the middle of prenatal development, the dental lamina loses the connection to oral epithelium after initiation of the second generation. In python, the ribbon-like lamina forms up to four generations of successional teeth and maintains the connection to oral epithelium in the pre-hatching period. Our previous study on snakes provided evidence that expression of *Shh* is first confined to the odontogenic band and defines the position of the future dental lamina (Buchtova et al., in press). Based on studies in snakes as well as work done by others on shrews and mice, we predict that *Shh* expression in pigs will first be detected in the odontogenic band. However unlike mice but similar to the snake, we expect to see prolonged expression in the oral–dental interface. Because pig fetus has a second generation of teeth developing just as humans, they represent an important mammalian model system for identifying the key signals needed to initiate the successional teeth.

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Program/Abstract # 137
Characterization of Tmem16f in vertebrate development
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TMEM16F is one of the ten homologues in the mouse and human TMEM16 family of proteins, a structurally related group of proteins